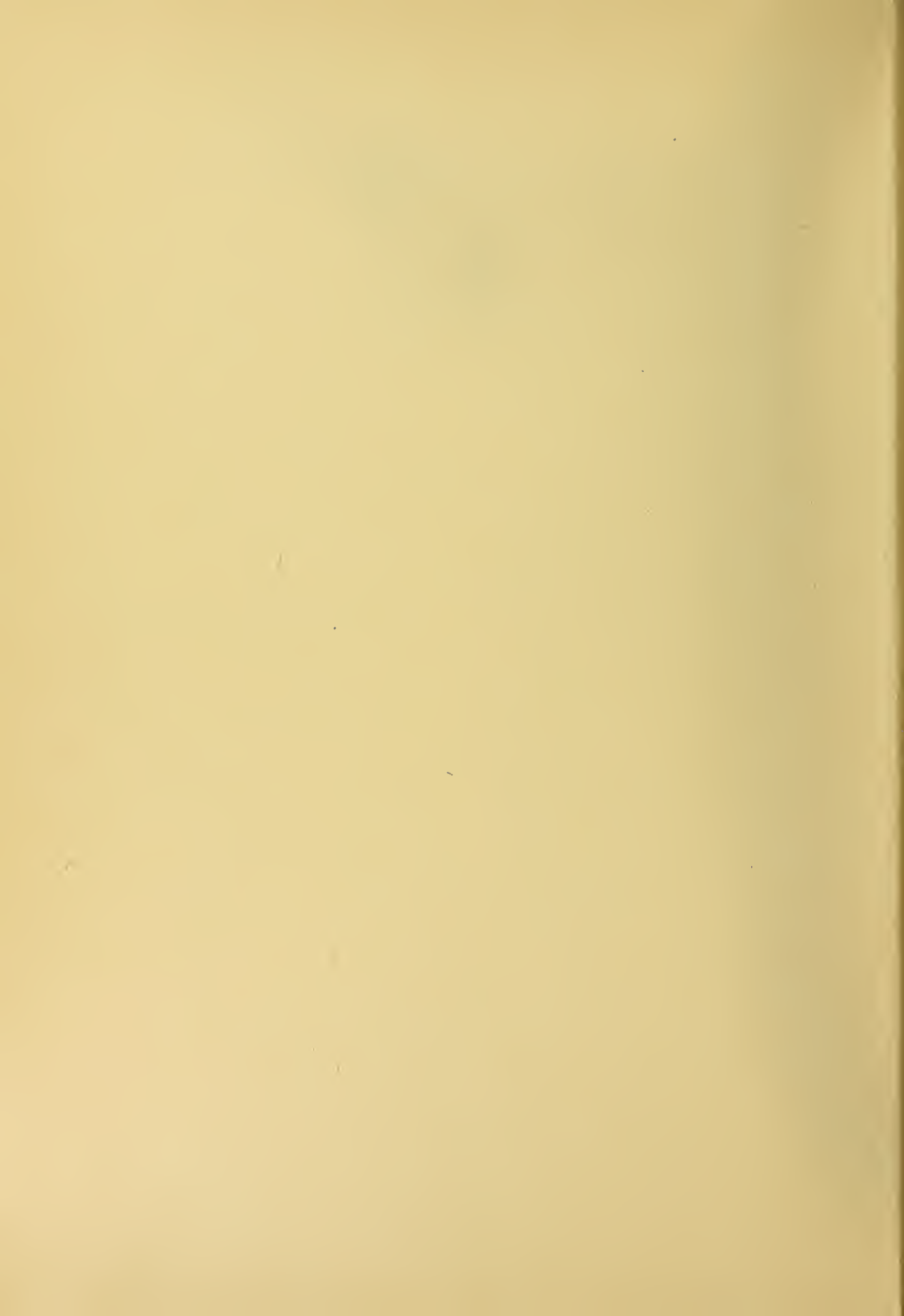


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ARTIFICIAL MUSKS:
THE STABILITY OF THE ISOPROPYL
GROUP IN CYMENE AND ITS
DERIVATIVES

BY

MORIS HOWARD JOFFE

THESIS

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

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IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science

in Chemical Engineering

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Chemistry



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INTRODUCTION AND HISTORICAL

Most of the expensive perfumes are unstable; the fragrance will not last. Quite accidentally it was found that a small portion of 'musk' will prevent decomposition and will even increase the strength of the fragrance. Musk, then, find their chief use in the perfume industries. Natural products which are obtained with difficulty and are expensive always form an incentive towards the preparation of synthetic or artificial products.

When one speaks of a synthetic or artificial product one naturally surmises that the synthesized compound has the same composition as the natural product. With artificial musks, however, this does not apply. Natural musks have been studied, yet little is known as to their structure. It has been determined that the active principle is of a ketonic structure and that it contains no nitrogen. The artificial musk is a nitro-derivative of the benzene series and resembles the natural product in odor only.

Among the foremost of investigators in synthesizing artificial musks was Albert Bauer. Together with Thurgan he synthesized tri-nitro-pseudo butyl toluene, tri-nitro pseudo butyl meta xylene¹, methyl ether of tri-nitro oxy pseudo butyl methyl benzene,² dinitro tertiary butyl xylyl methyl ketone, methyl ketone of tri-

1. B. 24, 2832-2843

2. B. 27, 1614-1619

nitro pseudo butyl toluene³ and di-nitro tertiary butyl xylyl aldehyde⁴. All of these compound smell strongly of musk. His work was followed by many others and numerous patents, both in Germany and France were issued for the preparation of artifical musks.

The object of this research is to prepare a product having a strong odor of musk, using cymene as the base; cymene being chosen because of its comparative cheapness.

3. B. 31, 1344-1349

4. B. 32, 3647-3648

THEORETICAL

Following along the line of work done by Baur and Thurgan, the methyl ketone of cymene was prepared¹. In the first runs the yield was very poor but by using a mercury seal stirrer and a three-necked flask, which made possible the introduction of the acetyl chloride slowly, the product was obtained with a yield of 62%. In large runs extreme care had to be exercised because of the large amount of carbon bisulphide used as a solvent. This ketone was then nitrated. For nitration purposes, in synthesizing ketone musks, Baur used 100 % nitric acid. Although 100 % acid, as a nitrating agent is not used now, it was thought advisable to make a run using Baur's method. Being unable to obtain the acid its preparation was tried, but the attempt proved unsuccessful. The problem was referred to the research department of the General Chemical Company, but was reported as a failure. This means of nitration had to be given up and instead, 7 % fuming sulphuric acid followed by fuming nitric acid was used.

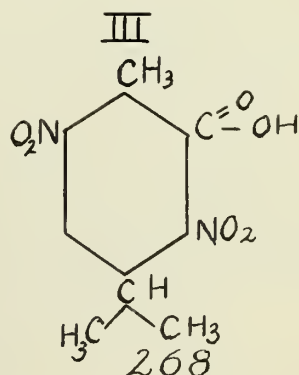
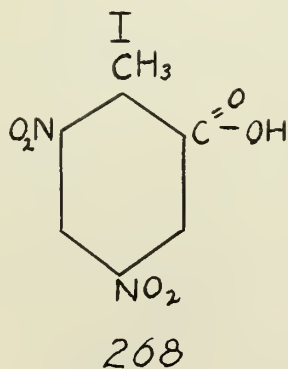
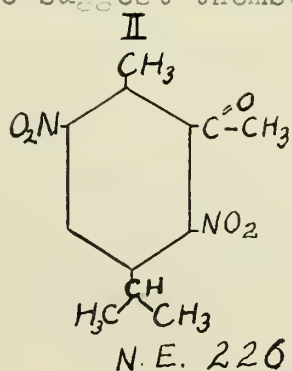
The results obtained by nitration^{of} acetocymene were very discouraging. All of Baur's compounds possessed a definite crystalline form. Acetocymene, however, on nitration came down as a gummy mass, which could not be crystallized from alcohol, petrol-^{um} ether, benzene, ethyl acetate or a mixture of ethyl acetate and benzene. The mass was set aside for six weeks and then a crystalline compound isolated from carbon tetrachloride. It was thought that this compound was a mono or dinitro derivative of acetocymene,

but tests showed that the compound was an acid, giving a definite neutral equivalent. This fact seemed so out of the ordinary that the preparation of further artificial musks was given up and the determination of the structure of this compound undertaken.

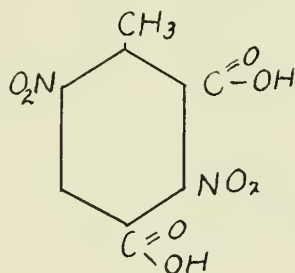
The nitration of acetocymene was repeated to obtain the yield of crystalline product. Attempts to isolate a solid from carbon tetrachloride immediately after nitration failed. It seemed that some "aging" is required before a separation can be made.

In 1920 Alfthan¹, a German chemist, studied the nitration products of cymene and toluene. He found that cymene on nitration gave 2,6 dinitrocymene and also 2,4 dinitro toluene. In the latter case the iso-propyl group is first oxidized to the acid and then the carboxyl group is replaced by a nitro group. He also found that *p*-acetotoluene upon nitration gave 2,6 dinitro-*p*----- toluic acid.

The product which was obtained by nitrating acetocymene dissolves in sodium hydroxide and gives a neutral equivalent. From previous work on cymene the following possibilities for its structure suggest themselves.

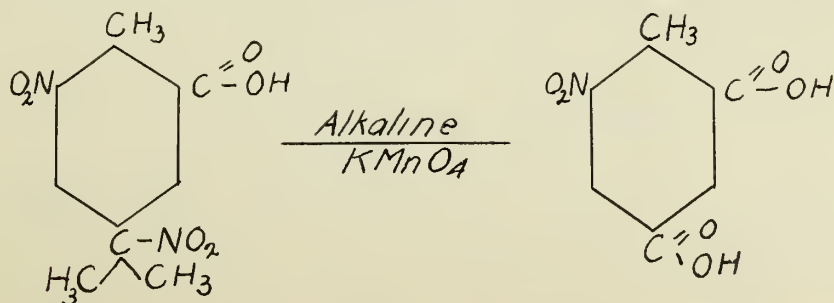


All three possibilities contain two nitro groups. The analysis for nitrogen clearly verifies this assumption. The neutral equivalent of 263, that was obtained eliminates formula I. The analysis for C eliminates formula II; formula III then remains. The nitrated product was oxidized using potassium permanganate in alkaline solution as the oxidizing agent. A white crystalline product melting sharply was obtained. A neutral equivalent was taken which showed the presence of two carboxyl groups. If formula III were correct the oxidation product should be



From previous work it has been shown that the isopropyl group is unstable and will be oxidized first. An analysis of the oxidation product showed the presence of only one nitro group and the neutral equivalent and the analysis for carbon did not check with the above formula. The only other possibility is that one nitro group has entered the isopropyl group, which on oxidation was removed.

The following structure was assigned to the crystalline product isolated from the nitration of acetocymene. All analysis verify



this assumption.

The stability of the isopropyl group in all of the previous work was not of the same degree. The author set out, therefore, to determine what properties or conditions were necessary to make the isopropyl group in cymene or its derivatives stable towards the action of the nitrating agent, sulphuric acid-nitric acid.

p-cymene treated with chlorine forms monochloro-cymene.¹ This on nitration gives 2-chloro-dinitrocymene. The yield was high, although a small amount of oxidation product was obtained. Again, when ^htymol was nitrated², trinitro-~~thymol~~ was not obtained. Instead, the isopropyl group was removed forming trinitro-m-cresol. Mr. Zellhoefer, of our laboratories, nitrated the methyl ether of ^htymol and obtained the methyl ether of tri-nitro-m-cresol.

These works as well as the work on cymene led to the belief that the group meta to the isopropyl group had some definite relation to the stability of that group. So many ideas have been set forth that nothing definite has as yet been determined along this line. With these points in view the second step in this research was begun.

Since the $-\text{COCH}_3$ group in acetocymene on nitration was oxidized to the carboxyl group the first step was to prepare o-methyl-m-isopropyl benzoic acid from acetocymene. A strong

1. J. Ind. and Eng. Chem. 11, 1130-1133

2. Chem. News 47, 115

strong oxidizing agent could not be used because of the instability of the isopropyl group. Directions are given in Noyes laboratory Manual for the oxidation of benzalacetone to cinnamic acid by using sodium hypochlorite as the oxidizing agent. By following these general directions with the exception that a more concentrated hypochlorite solution was used it was possible to oxidize acetocymene to o-methyl-m-isopropyl benzoic acid in yields exceeding 75 %. This acid has previously been prepared¹ by heating tricarvacrol phosphate with potassium cyanide and then hydrolyzing the product. This reaction is accompanied by the formation of many impurities which make it much more complicated than the method used above.

The acid thus obtained was then nitrated under the same conditions that acetocymene was nitrated. A pale yellow compound was obtained which upon recrystallization from 50% alcohol came down in very fine needles, clustering to form plates. A mixed melting point with the nitration product of acetocymene gave a melting point which was the same as that of the original compound. There is no doubt that the compound obtained from the nitration of acetocymene and from the nitration of o-methyl-m-isopropyl benzoic acid are the same. There is, however, a marked difference in the yields of these products. The first was obtained with difficulty with a yield of 15%, while the second was obtained with a yield of 92%. Here we have evidence, surely, of a stabilizing action.

1. B. 18, 1714

It seems highly probable that the carboxyl group meta to the isopropyl group stabilizes that group towards the action of the nitrating agent.

To further verify the assumption that the $-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\text{O}$ stabilizes the isopropyl group the methyl ester of o-methyl-meta-isopropyl benzoic acid was nitrated. The o-methyl-m-isopropyl benzoyl chloride was first prepared and this on treatment with absolute methyl alcohol gave the ester.

The ester, like acetocymene, is ^a high boiling liquid; the characteristic properties of these two compounds are closely related. Yet, aceto-cymene on nitration forms a gummy mass from which a definite crystalline compound is obtained with difficulty, while the ester when nitrated under exactly the same conditions, reacts very smoothly forming a well crystallized product. The difference in behavior of these two compounds can be explained by the stabilizing action which the $-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\text{O}$ group meta to the isopropyl group has towards that group.

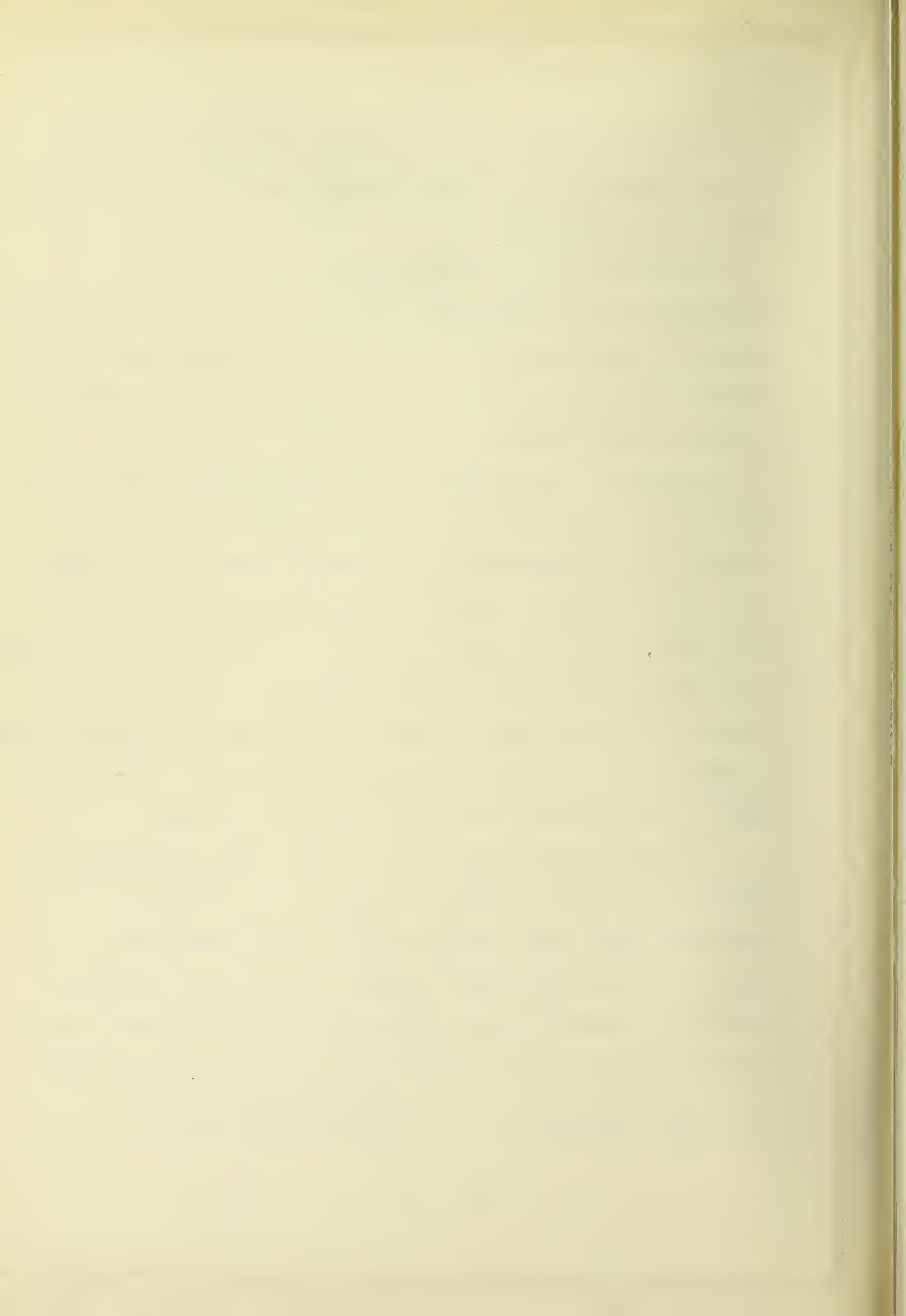
Alfthan¹ in his article states that 2,3,6 trinitrocymene has been obtained by nitrating cymene. R. Fittig² obtained a 'trinitrocymene' which melts at 119°. Zaloziecki³ also isolated a 'trinitrocymene' melting at 126°, while Landolf⁴ obtained a compound which he also calls trinitrocymene melting at 183.5°-184.5°. It is the belief of the author that cymene

1. B. 53B, 180

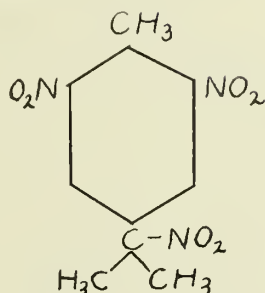
2. A. 145, 142(1863)

3. B. 27, 2085

4. B. 6, 938 (1873)



on nitration forms dinitrocymene and that on further nitration the third nitro group enters the side chain forming a compound with the following structure.



The 2,6 dinitrocymene was prepared and then nitrated. The reaction did not proceed smoothly.

In connection with the preparation of acetocymene several runs were made to determine whether aluminum chloride in the Friedel and Craft's reaction adds on as AlCl_3 or as Al_2Cl_6 . If it adds on as Al_2Cl_6 two mols would have to be used to obtain the product. Two runs using first one mol and then two mols of aluminum chloride gave yields of 41% and 41.5% . Without a question only one mol is necessary in the above reaction.

Butyl derivatives of the benzene series, especially toluene and xylene, when nitrated form very good artificial musks. The introduction of a tertiary butyl group into cymene by the Friedel and Craft's reaction using aluminum chloride was tried but very poor yields were obtained. In a recent review on artificial musks¹ the authors state that to introduce the butyl group into the benzene ring ferric chloride should be used instead of

1. Chemie and Ind. 6, 719

aluminum chloride. The failure to prepare tertiary butyl cymene is then accounted for.

Acetomesitylene was prepared and this product nitrated gave a compound with a musk odor.

EXPERIMENTAL

p-Cymol methyl ketone, acetocymene

To 480 gr. of cymene (10 mols) 2000 c.c. of carbon bisulphide was added. The mixture was kept in an ice bath. To this 440 gr. of pulverized aluminum chloride was slowly added. After the reaction ceased 280 gr. (10 mols) of acetyl chloride was added drop by drop, the mixture being vigorously stirred by means of a mechanical stirrer. The whole was allowed to reflux for two to three hours until all the hydrochloric acid evolved came over. The carbon bisulphide was then quickly distilled and the residue poured over ice water to remove the aluminum chloride. The dark brown oil was separated and extracted with ether. The ether solution was washed with water and then dried over calcium chloride. The dry ether solution was then distilled. A clear, yellow, sweet smelling oil boiling at 256° - 260° , uncorrected, was obtained. Yield 392 gr., 62%.

Nitration of Acetocymene

To 20 gr. of acetocymene, kept at 0° C., 66 gr. of 7% fuming sulphuric acid was slowly added. The ketone slowly changed its color until quite dark brown on addition of all the acid. To this solution 34 gr. of fuming nitric acid (sp. gr. 1.50) was added at the rate of 30 drops per minute, a mechanical stirrer being used. After all of the acid was added the nitration was allowed to proceed for another two hours.

A dark brown mass was obtained which was poured over ice water and thoroughly washed from all acids. The final product which was light yellow in color formed a gummy mass. After standing six weeks a crystalline compound was isolated from carbon tetrachloride. Yield 3 grams.

Analysis of Nitration Product

Subs. O.1986; 6.35 c.c. of 0.1187 N. NaOH required.

Subs. O.2500, O.4000; CO₂; 266.8 c.c., 428 c.c.; Temp. 26°, 23° C.; Pressure: 741.7 mm., 734.2 mm.

Subs. O.2090; N: 20.4 c.c.; Temp.: 24° C.; Bar. 741 mm.

Calc. for C₁₁H₁₂O₆N₂: C, 49.2; N: 10.42; N.E. 268

Found:---- C: 49.23; N: 10.71; N.E. 263

M.P. 182.5°, 183.5°, 183⁵¹°.

Oxidation of Nitrated Compound

1 gram of the nitrated product was dissolved in 10 c.c. of 10% sodium bicarbonate solution. To this 5.5 gram of potassium permanganate, dissolved in water containing 3 c.c of 10% sodium hydroxide, was added. The mixture was allowed to reflux for twelve hours. At the end of this period the manganese dioxide was filtered off and any impurities soluble in ether removed. The residue was acidified with dilute sulphuric acid and the product extracted with ether. The ether was distilled off and the product recrystallized from hot water. It came down in fine white needles melting at 199° - 200° C.

Analysis

Subs: 0.23275; 22.14 c.c. of 0.0909 N KOH required.

Subs: 0.3014 gr.; CO₂, 310 c.c.: Temp. 21.8° C., Bar. 740.5 mm.

Subs: 0.1932; N: 10.4 c.c.; Temp. 25° C.; Bar. 746.8 mm.

Calc. for C₉H₇O₆N: N.E., 112.5; C: 48; N: 6.22

Found : N.E., 115.5; C: 48.27; N: 5.93

o-Methyl-m-Isopropyl Benzoic Acid

To 450 gr. of chloride of lime 600 c.c. of water was added. To this 550 gr. of sodium carbonate in 650 c.c. of water was added. The mass was filtered and washed once. The filtrate was added to 50 gr. of acetocymene and the whole refluxed for four hours, keeping the temperature at 80° - 90° C. A mechanical stirrer was used. At the end of the reaction, shown by the disappearance of the oily layer, the mixture was cooled and the uncombined acetocymene extracted with ether. The residue was acidified with dilute sulphuric acid, the produce extracted with ether and then recrystallized from 50% alcohol. It came down in white needles clustering into plates. M.P. 75° C. Yield 27.5 gr. 55%. 15 gr. of acetocymene was recovered, making an actual yield of 78.5 %.

Nitration of o-methyl-m-isopropyl benzoic acid

To 5 gr. of the acid, kept at 0° C. 17 gr. of 7% fuming sulphuric acid was slowly added, which seems to dissolve the product, forming a brown mixture. To this mixture 8 gr. of fuming nitric acid (sp. gr. 1.50) was added drop by drop. On

addition of the nitric acid the mixture gradually changed to a lemon yellow color. It was allowed to nitrate for one hour after all of the nitric acid was added, and then poured over ice water and thoroughly washed. Upon recrystallization from 50% alcohol it came down in fine white crystals melting at 182° C. A mixed melting point with the product isolated from the nitration of acetocymene gave a melting point of 182° . No gummy mass was formed.

o-Methyl-m-isopropyl benzoyl chloride

To 5 gr. of o-methyl-m-isopropyl benzoic acid 6 gr. of finely pulverized phosphorous pentachloride was added. The reaction began after shaking vigorously and heating slightly on the steam bath. A dirty yellow liquid was formed which was distilled under diminished pressure from an oil bath. The excess phosphorous pentachloride distilled over first and was removed. A light greenish yellow, clear liquid having a sharp odor and boiling at 133° (25 mm.) was obtained.

Yield 2.5 gr., 45.4%

Analysis of Product

To 15 c.c. of absolute ethyl alcohol a definite amount of the chloride was added. To this solution 1 gr. of sodium was added, and the whole refluxed on the steam bath for a half hour. A milky white liquid was obtained. The alcohol was distilled off and the residue diluted with 20 cc. of water containing 2 c.c. of

conc. HNO_3 . The solution was titrated with standard silver nitrate using ferrous sulfate as the indicator.

Subs: 7539, 42.3 c.c. of 0.0981 N AgNO_3 required.

Calc. for $\text{C}_{11}\text{H}_{13}\text{OCl}$: Cl: 19.29%. Found Cl: 19.51%

Methyl Ester of o-methyl-m-isopropyl benzoic acid

To 7 gr. of the acid chloride 10 c.c. of absolute methyl alcohol was added, and the whole refluxed for eight hours. The liquid obtained was distilled under diminished pressure using an oil bath. A clear, colorless liquid having a very pleasant odor and a boiling point of 132° (10 mm.) was obtained.

Yield 5.9 gr. 86.8%.

Nitration of the methyl ester of O-methyl-m-isopropyl benzoic acid

To 5.9 gr. of the ester 19.7 gr. of 7% fuming sulphuric acid was slowly added, keeping the solution at 0°C and well stirred. No change in the solution was noticed. To this 9.8 gr. of fuming nitric acid (sp.gr. 1.50) was added at the rate of 30 drops a minute. The solution first became orange yellow then light yellow and viscous as more acid was added. After the addition of the nitric acid the mixture was allowed to nitrate for another hour. At the end of this period it was poured over ice and thoroughly washed until free from acids. It was recrystallized from 50% alcohol coming down in clustering needles which were white when freshly formed, but which turned orange on

standing. M.P. 161° , but not definite. No sticky mass, as in the nitration of acetocymene, was formed.

2,6 Dinitrocymene

To 25 gr. of p-cymene 100 gr. of sulfuric acid (sp. gr. 1.84) was slowly added. The solution was cooled by salt-ice mixture and well stirred by a mechanical stirrer. On addition of the acid the solution became yellow. To this 50 gr. of fuming nitric acid (sp. gr. 1.50) was added drop by drop. The solution became dark brown. It was allowed to nitrate for two hours. At the end of this period it was poured over ice water. It came down as a sticky brownish mass which was extracted with ether and thoroughly washed with water until free from acids. To the ether solution 50 c.c of 10% sodium bicarbonate solution was added. Any acids that may have formed were thus removed. The ether soluble portion was again washed and then dried over CaCl_2 . The ether was distilled off leaving a clear, rather viscous, reddish liquid. Yield 25 gr., 59.7%.

Analysis

Subs. 0.4148; 493.6 c.c. CO_2 ; Temp. 30.2° ; Bar. 741.3

Calc. for $\text{C}_{10}\text{H}_{12}\text{O}_4\text{N}_2$: C: 53.57%; Found: C: 53.51%

Nitration of 2,6 Dinitrocymene

To 10 gr. of dinitrocymene 33 gr. of 7 % fuming sulfuric acid was added. The solution first became light yellow but turned to dark brown on addition of all of the acid. To this 17 gr. of fuming nitric acid (sp. gr. 1.50) was added drop by drop. The

color gradually changed to yellow. After nitrating for an hour the product was poured over ice water. It came down as a gummy mass. A solid was isolated from carbon tetrachloride which melted at approximately 210° . The yield was poor.

Acetomesitylene

50 grams of mesitylene was dissolved in 200 c.c. of carbon bisulphide, to which was added 125 gr. of freshly distilled acetyl chloride. By using a three necked flask 50 gr. of finely pulverized aluminum chloride was added just fast enough to keep the reaction going. The mixture was mechanically stirred and allowed to react for one hour. The carbon bisulphide was then quickly distilled and the residue poured over ice water. The oil was extracted with ether, washed, then dried over calcium chloride and distilled. A light yellow, clear liquid boiling at 235° - 237° (uncorrected) was obtained. Yield 48 grams., 72%. The reaction should not be allowed to proceed for more than one hour, and the aluminum chloride must be added slowly to obtain a product with yields over 70%.

Nitration of Acetomesitylene

To 10 gr. of acetomesitylene 34 gr. of 7% fuming sulfuric acid was added. To this solution 17 gr. of fuming nitric acid (sp. gr. 1.50) was added drop by drop. After nitrating for an hour the product was poured over ice water and thoroughly washed. It was extracted with ether and the ether then evaporated. A light brown solid melting at 193° with darkening was obtained.

SUMMARY

I. Acetocymene was prepared and then nitrated using 7% fuming sulfuric acid and fuming nitric acid(sp. gr. 1.50) as the nitrating agent. A crystalline compound was isolated with difficulty.

II. The structure of this compound was determined. The $-\text{COCH}_3$ group, was oxidized to the carboxyl group, one nitro group entered the side chain in the isopropyl group and one nitro group entered the ring.

III. o-Methyl-m-isopropyl benzoic acid was prepared and then nitrated under the same condition as acetocymene. The nitration products of both were the same, the yield in the latter, however, was much greater.

IV. The methyl ester of O-methyl-m-isopropyl benzoic acid was nitrated as above and a solid compound obtained without the formation of side products.

V. Some evidence was collected which indicated that the $-\text{C}(=\text{O})-\text{O}$ group, meta to the isopropyl group, stabilizes that group towards the action of the nitrating agent sulfuric acid--nitric acid.

VI. Acetomesitylene was prepared and then nitrated. A compound smelling of musk was obtained.

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